EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Compliance and Inspection

Results of the sampling and testing programme for the year 2011

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Executive summary

This report concerns the 2011 Sampling and Testing Programme coordinated by the EMA in accordance with Regulation (EC) 726/2004, art. 57(r). A total of 38 products were sampled and tested, which required the cooperation of 32 inspectorates (for the sampling) and of 27 official laboratories for the testing. The large majority (89%) of products tested complied with the authorised specifications; 4 products were found to be out of specification. Suitable investigations took place in order to address these suspected quality defects.

In addition to the routine programme, in 2011 a specific programme for generic medicinal products was piloted. Upon the request of the Committee for Human Medicinal Products, centrally authorised generics of clopidogrel film-coated tablet were targeted. The products were sampled by 12 inspectorates, and testing was carried out by 3 official laboratories.

Testing was completed for a veterinary product that had originally been included in the 2010 Programme. Results showed that one parameter appeared to be outside the authorised specification. The results however could not be verified because the quantity of product available was not sufficient to repeat the testing. Re-sampling and testing of this product is currently being planned.

The 2011 programme included a pilot scheme to carry out some checks on the printed packaging materials of the samples taken, to verify the compliance of the main information of the label and of the package leaflet (PL), with the authorised texts.

The sampling and testing programmes

Legal basis

Regulation (EC) 726/2004, art. 57(r) – The Agency shall provide the Member States and the institutions of the Community with the best possible scientific advice on any question relating to the evaluation of the quality, safety and efficacy of medicinal products for human or veterinary use which is referred to it in accordance with the provisions of Community legislation relating to medicinal products. To this end, the Agency, acting particularly through its committees, shall undertake the following tasks:

(r) coordination of the supervision of the quality of medicinal products placed on the market by requesting testing of compliance with their authorised specifications by an Official Medicines Control Laboratory or by a laboratory that a Member State has designated for that purpose;

Scope of the programmes

The main aim of the programmes is to verify that the centrally authorised medicinal products on the market comply with their authorised quality specifications. Additionally, this monitoring activity allows for a practical assessment of the analytical methods themselves used by the manufacturers for the control of the products.

Partners

The success of the programmes is based on the cooperation and partnership of the following:

European Medicines Agency (EMA) - overall management
European Directorate for the Quality of Medicines and HealthCare (EDQM) - coordination of the sampling and of the testing, and reporting
Network of Official Medicines Control Laboratories (OMCLs) in the EEA - testing
Inspection Services of the EEA National Competent Authorities - sampling from the market
EMA Scientific Committees (CHMP and CVMP) - adoption of the programmes
Products' Rapporteurs and CoRapporteurs - advice on testing recommendations and follow-up actions

Report on the 2011 programme

Preparatory work

Lists of products to be tested were prepared by the Compliance and Inspection Sector on the basis of a risk-based approach[1]. The lists were submitted to the CHMP and the CVMP in February 2010, and were adopted by the relevant Committee. For the list of the products tested, see Annex 2.

Once the lists were endorsed and finalised the Manufacturing and Quality Compliance Section wrote to the Marketing Authorisation Holders (MAHs) of the selected products. They were informed of the inclusion of their products in the testing programme, and asked to provide the documentation and the material needed to carry out the testing.

Advice on the parameters to be tested for each product was obtained from the relevant Rapporteurs.

Sampling

Samples of the products[2] were drawn by inspectors of the competent national authorities, from their respective national markets. When possible, each product was sampled in three different Member States. Below is a table summarising the sampling phase.

Number of products	Number of inspectorates	Number of samples taken	Number of samples taken from the Parallel Distribution market
38	32	113	1

Generic pilot programme

Number of products	Number of inspectorates	Number of samples taken	Number of samples taken from the Parallel Distribution market
6	12	13	0

[1] Proposal for development of risk based approach for human products (EMA/INS/S&T/81176/2007)
Proposal for development of risk based approach for veterinary products EMA/INS/S&T/75010/2009)
[2] For the purpose of the figures contained in this report, a 'product' can include 2 or more medicinal products (with different Marketing Authorisation numbers) which are identical. See also list in Annex 2.

Label and PL checks

Label and PL checks were carried out by the samplers. A checklist was provided to the samplers to assist in this process. The outcome of these checks is reported in Annex 1 of the relevant testing reports.

Number of Labels/PLs checked	Suspected non-compliances identified [3]
55	5

The purpose of the exercise was not to perform a full label and PL check of compliance, but rather to highlight potential issues for further investigation.

Testing

Testing of the products started in March 2011. Chemical products and insulin analogues were tested in one laboratory only. When needed, a back-up laboratory was available. Biological products were tested in two laboratories. In one case, testing of a parameter required a specific equipment. This equipment was only available at Swissmedic, who agreed to carry out this test free of charge. Below is a table summarising the testing phase.

Number of products tested	Number of Laboratories
38 (total)	27

Generic pilot programme

Number of products tested	Number of Laboratories
6	3

Reporting

The EDQM prepared and sent CAP testing reports (one for each product) containing details of the testing results to the EMA on an on-going basis. Results were classified in a 1 – 4 scale, according to the testing outcome. Below is a table summarising the results.

Products tested	1 = No problems identified	2 = Issues identified	3 = Out of specification	4 = Out of specification (Health risk)
Total = 38	15	19	4	0
Human = 30	12	16	2	0
Veterinary = 8	3	3	2	0

Generic programme

Products tested	1 = No problems identified	2 = Issues identified	3 = Out of specification	4 = Out of specification (Health risk)
Human = 6	6	0	0	0

[3] for which a Quality Defect procedure was initiated

Report circulation

The testing reports were first circulated to the respective Marketing Authorisation Holder, with the request to provide their comments.

The comments from the MAHs, and the reports, were then circulated to the Rapporteurs with the request to provide advice for follow-up

Outcome

Most of the problems identified during the testing were in relation to the detail of the analytical procedures authorised or used for the control of the medicinal products. In order to address these issues, the Manufacturing and Quality Compliance Section had extensive contacts with the MAHs, which resulted in most of cases, in the MAH submitting a variation application.

For products reported to be `out of specification`, a Suspected Quality Defect procedure was initiated. Recall of the batches was proposed and performed by the MAH for one product. The quality of the other products was judged to be satisfactory, the problems being attributed to the testing method.

Conclusion

The results of the 2011 Programme showed that most of the products tested were in compliance with the authorised specifications, with four products found to be outside their specifications.

In view of the results obtained in the 2011 Sampling and Testing Programme, it can be concluded that this annual monitoring exercise continues to be an important tool in the implementation of the EMA task of supervision of medicinal products placed on the market.

Annex 1: Acronyms

CAP:	Centrally Authorised Product
CHMP:	Committee for Medicinal Products for Human Use
CVMP:	Committee for Medicinal Products for Veterinary Use
EDQM:	European Directorate for the Quality of Medicines and HealthCare
EEA:	European Economic Area, formed by the Members of the European Union and Iceland, Liechtenstein and Norway
MAH:	Marketing Authorisation Holder
OMCL:	Official Medicines Control Laboratory
PL:	Package Leaflet

Annex 2: List of products tested in the 2011 programme

	Product	**Pharmaceutical form**
1	Abraxane	Powder for suspension for infusion
2	Abseamed /Epoetin alfa Hexal /Binocrit	Solution for injection in a pre-filled syringe
3	Actrapid	Solution for injection
4	Aldurazyme	Concentrate for solution for infusion
5	Angiox	Powder for concentrate for solution for injection or infusion
6	Aprovel	Tablet
7	Atripla	Film-coated tablet
8	Circadin	Prolonged-release tablets
9	Clomicalm	Tablet
10	Docefrez	Powder and solvent for concentrate for solution for infusion
11	Efficib/Velmetia/Janumet	Film-coated tablet
12	Equilis StrepE	Lyophilisate and solvent for suspension for injection
13	Filgrastim Hexal/Zarzio	Solution for injection or infusion
14	Humira	Solution for injection
15	Improvac	Solution for injection
16	Integrilin	Solution for injection
17	Leucofeligen FeLV/RCP	Lyophilisate and solvent for suspension for injection
18	Myocet	Powder and pre-admixtures for concentrate for liposomal dispersion for infusion
19	Myozyme	Powder for concentrate for solution for infusion
20	NovoMix	Suspension for injection
21	Nplate	Powder for solution for injection
22	Optisulin /Lantus	Solution for injection
23	Porcilis Porcoli Diluvac forte	Suspension for injection
24	Quadrisol	Oral gel
25	Rebif	Solution for injection
26	ReFacto AF	Powder and solvent for solution for injection
27	Retacrit/Silapo	Solution for injection
28	Revlimid	Hard capsule
29	Soliris	Concentrate for solution for infusion
30	Somavert	Powder and solvent for solution for injection
31	Suvaxyn Aujeszky 783 + O/W	Emulsion for injection after reconstitution
32	Tandemact	Tablet
33	Tasigna	Hard capsule
34	Tevagrastim	Solution for injection or infusion
35	Tysabri	Concentrate for solution for infusion
36	Zactran	Solution for injection
37	Zebinix	Tablet
38	Zeffix	Oral solution

Generic products

	Product	**Pharmaceutical form**
1	Clopidogrel ratiopharm/ Clopidogrel ratiopharm GmbH/ Clopidogrel Sandoz	Film-coated tablet
2	Clopidogrel Krka/ Clopidogrel Mylan/ Clopidogrel Teva Pharma	Film-coated tablet
3	Clopidogrel Apotex/Grepid	Film-coated tablet
4	Clopidogrel Teva	Film-coated tablet
5	Clopidogrel Zentiva	Film-coated tablet
6	Plavix (Control Test Sample)	Film-coated tablet

Annex 3: List of inspectorates participating in the 2011 programme[4]

Country	**Name**
Austria	Ages PharmMed
Belgium	Agence Federale Des Medicaments Et Produits De Sante
Bulgaria	Institute for Control of Veterinary Medicinal Products
Czech Republic	State Institute For Drug Control Institute State Control Of Veterinary Biologicals
Cyprus	Ministry Of Health
Denmark	Danish Medicines Agency
Estonia	State Agency of Medicines
Finland	Finnish Medicines Agency – FIMEA
France	Afssaps Anses – Anmv
Germany	Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten – ZLG
Greece	National Organization for Medicines
Hungary	Central Agricultural Office, Directorate Of Veterinary Medicinal Products National Institute Of Pharmacy
Iceland	Icelandic Medicines Control Agency
Ireland	Irish Medicines Board
Italy	Ministerio Della Salute – AIFA
Lithuania	State Medicines Control Agency, Ministry Of Health
Luxembourg	Ministère de la Santé, Division Pharmacie et Médicaments
Malta	Medicines Authority
The Netherlands	Inspectie voor de Gezondheidszorg Ministerie van Landbouw Natuur en Voedselkwaliteit
Norway	Norwegian Medicines Agency
Poland	Glowny Inspektorat Farmaceutyczny
Portugal	Instituto Nacional Da Farmacia E Do Medicamento - INFARMED Direccao Geral De Veterinaria
Romania	National Medicines Agency
Spain	Agencia Espanola De Medicamentos Y Productos Sanitarios
Slovenia	Agency for Medical Products and Medical Devices of the Republic of Slovenia
Sweden	Medical Products Agency
United Kingdom	Medicines And Healthcare Products Regulatory Agency - MHRA

[4] Source: EDQM

Annex 4: List of laboratories participating in the 2011 programme[5]

Country	**Name**
Austria	AGES-C - AGES PharmMed (Chemicals & Pharmaceuticals), Vienna
Belgium	VAR – Veterinary and Agrochemical Research Center, Ukkel IPH-C – Scientific Institute of Public Health – Medicines Section, Brussels
Cyprus	SGL – Laboratory for the Quality Control of Pharmaceuticals, Cosmetics and Food Suppl., Nicosia
Czech Republic	USKVBL - Institute for State Control of Veterinary Biologicals and Medicaments, Brno
Denmark	DKMA - Danish Medicines Agency, Copenhagen
Estonia	SAM – State Agency of Medicines, Quality Control Laboratory, Tartu
Finland	FIMEA – Finnish Medicines Agency/Laboratory, Helsinki
France	ANSM – Direction des Laboratoires et des Contrôles – Site de Montpellier (formerly AFSSAPS-M), Vendargues ANSM - Direction des Laboratoires et des Contrôles (formerly AFSSAPS-P), Site de Saint-Denis ANSES – Agence Nationale du Médicament Vétérinaire, Fougères
Germany	PEI – Paul-Ehrlich Institut, Langen AMI - Arzneimitteluntersuchungsinstitut –Nord GmbH, Bremen BY – Landesamt für Gesundheit und Lebensmittelsicherheit, Oberschleißheim
Hungary	NIP – Laboratory of National Institute of Pharmacy, Budapest DVMP – Central Agricultural Office – Directorate of Veterinary Medicinal Products, Budapest
Ireland	IMB_PALG – Public Analyst's Laboratory, Galway
Italy	ISS-H – Istituto Superiore di Sanità, Roma
Latvia	SAM – Medicines Examination Laboratory, Riga
Lithuania	VVKT – State Medicines Control Agency / Medicines Control Laboratory, Vilnius
The Netherlands	RIVM-B – Centre for Biological Medicines and Medical Technology, Bilthoven
Norway	NOMA – Norwegian Medicines Agency, Oslo
Poland	IL – National Medicines Institute, Warsaw
Portugal	INFARMED – I.P. National Authority for Medicines and Health Products, Lisbon
Sweden	MPA – Medical Product Agency, Uppsala
United Kingdom	NIBSC – National Institute for Biological Standards & Control, Potter's Bar MHRA – Laboratory of the Government Chemist, Teddington

[5] Source: EDQM